Drug/Drug Interactions in the Elderly

Bruce G. Pollock, M.D., Ph.D.

Self Assessment Question 1

- Compared to the rate of ADRs among adults age 20-29, the rate among adults age 80+ is which of the following:

A. Similar

B. Twice as great

C. Greater than 5 x as frequent

D. Greater than 10 x as frequent

Self Assessment Question 2

- Commonly prescribed psychiatric medications are substrates of which of the following C450 enzymes?

A. 1A2

B. 2D6

C. 3A4

D. All of the above

Self Assessment Question 3

- Which of the following 3A inhibitors can be associated with significant drug/drug interactions when co-administered with a 3A substrate?

A. Ketoconazole

B. Erythromycin

C. Calcium antagonists

D. Any of the above

Self Assessment Question 4

- Which of the following medications has anticholinergic properties?

A. Furosemide

B. Warfarin

C. Ranitidine

D. Digoxin

E. All the above

Self Assessment Question 5

- The risk of drug/drug interactions is increased by which of the following?

  A. Narrow therapeutic index of co-administered agent

  B. Highly potent co-administered enzyme inducer or inhibitor

  C. Greater sensitivity to adverse effects in elderly patients

  D. Co-administration of multiple drugs

  E. All the above

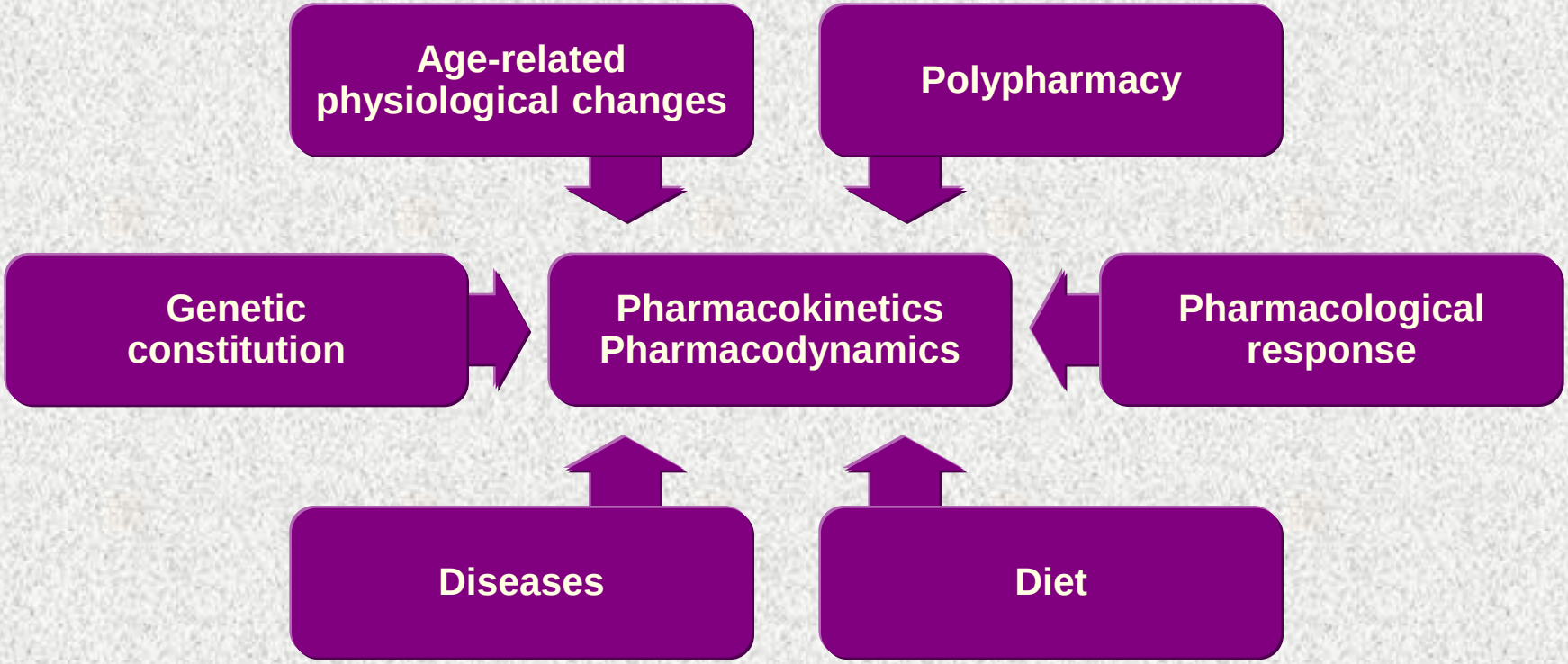
Major Teaching Points

- Elderly patients are highly vulnerable to drug/drug interactions
- Two important types of drug/drug interactions to understand and prevent are:
  - Pharmacokinetic interactions based on drug metabolism through the cytochrome P450 system
  - Pharmacodynamic interactions based on additive serum anticholinergicity

Brief Outline

- Adverse drug interactions' relationship to age, location, number of prescribed drugs
- Cytochrome P450 drug interactions
- Drug interactions based on additive serum anticholinergicity
- Coping with drug/drug interactions
- Suggested readings

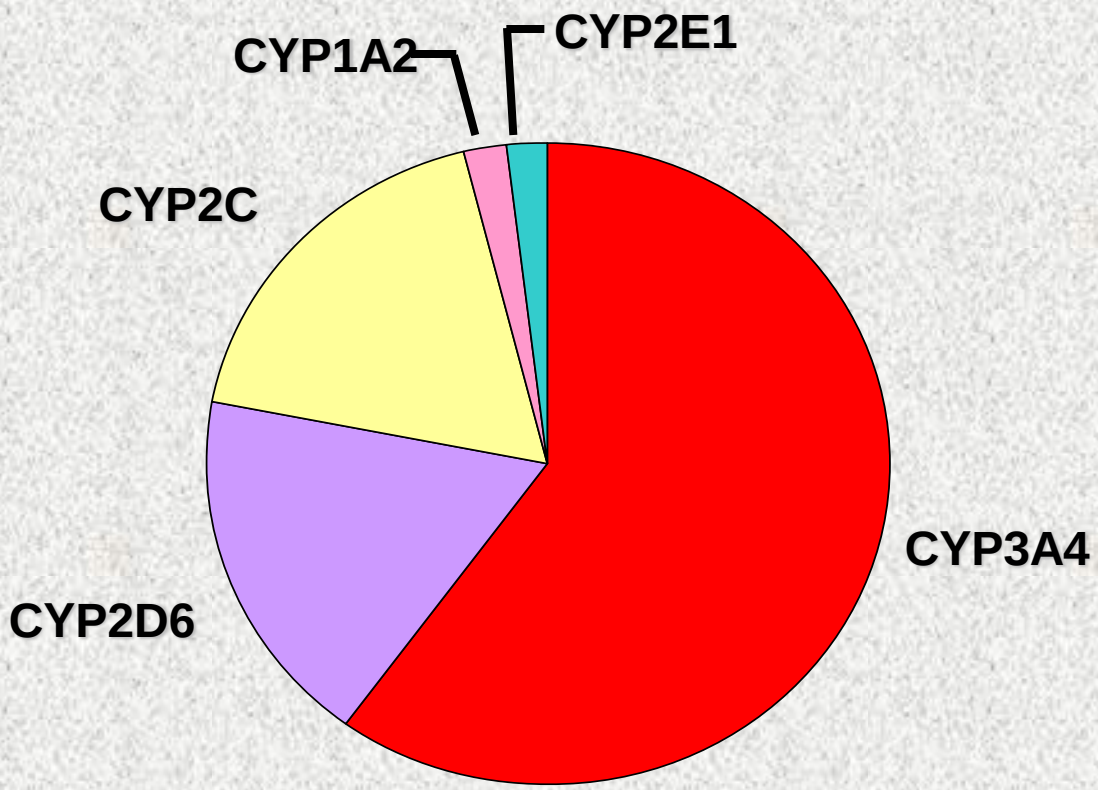
Factors Affecting Drug Response & Predisposing to Drug Interactions in the Elderly



Clinical Dilemma

- Number of possible drug interactions too large to memorize
- Difficult to determine which interactions are important
- Conflicting promotional claims

Cytochrome P-450 Enzyme Subtypes



CYP isoform	Representative substrates
1A2	Caffeine, theophylline, tacrine
2B6	Propofol, bupropion
2C9	Phenytoin, S-warfarin, tolbutamide, NSAIDs
2C19	Omeprazole (partial contributor to many)
2D6	Some CNS and cardiac drugs
2E1	Fluranes, chlorzoxane
3A	(many)

CYP3A

- High abundance
- Present in G.I Tract
- No polymorphism, but high individual variability

CYP3A Substrates

Complete	Partial
Benzodiazepines (short $t_{1/2}$)	Zolpidem
Buspirone	Amitriptyline
Trazodone	Imipramine
Nefazodone	Sertraline
Cyclosporine	Citalopram
Statins	Diazepam
Calcium antagonists	Clozapine
Quinidine	
Protease Inhibitors	
Sildenafil	

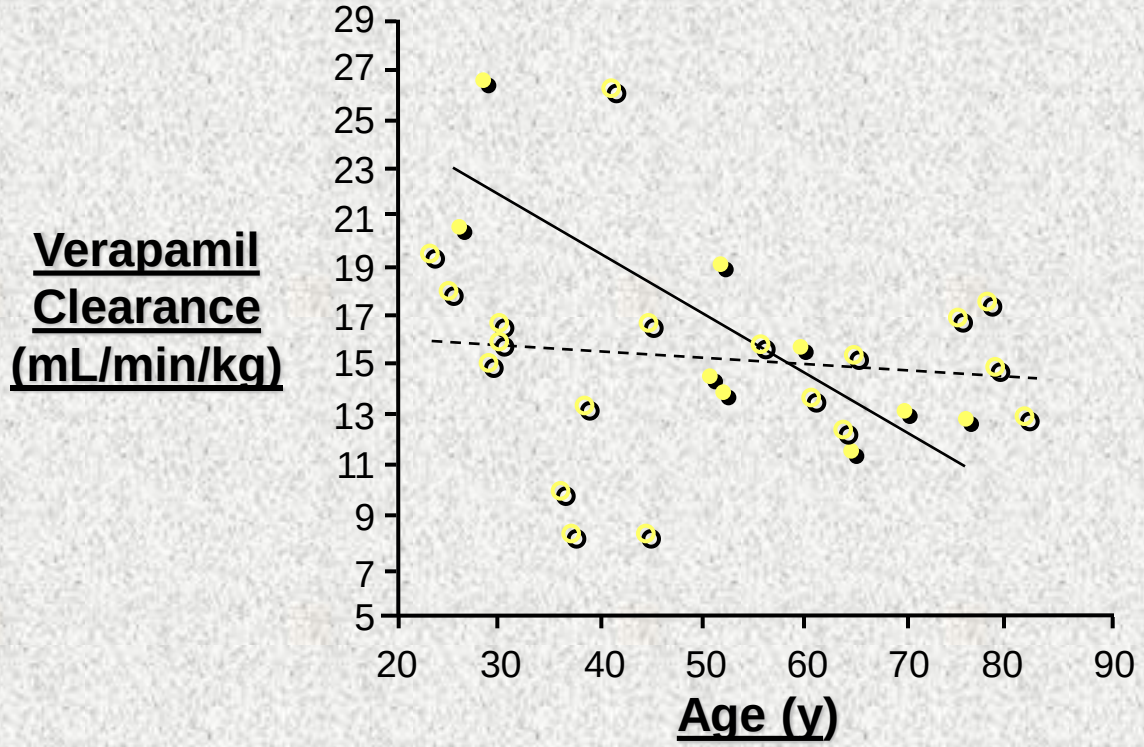
CY3A Inhibitors

High Risk	Moderate Risk
Ketoconazole	Fluconazole
Itraconazole	Fluvoxamine
Nefazodone	Fluoxetine
Ritonavir (acute)	Grapefruit juice
Erythromycin	Other HIV PIs
Clarithromycin	Delavirdine
Calcium Antagonists	Cimetidine

CYP3A Inducers

- Rifampin
- Barbiturates
- Carbamazepine
- Ritonavir (chronic)
- Nevirapine
- Hypericum perforatum (St. John's Wort)

CYP3A4: Verapamil



Racemic verapamil clearance data are plotted versus age for women (*solid circles*) and men (*open circles*). The *solid line* represents the regression of clearance versus age relationship in women ($P < .004$) and the *broken line* represents the regression of clearance versus age in men (regression not significant).

Schwartz JB, et al. *Clin Pharmacol Ther*. 1994;55:509-517.

St. John's Wort

- **Induces P-glycoprotein**
  - **↓ Digoxin by 30%**
- **Induces CYP3A4**
  - **↓↓ Indinavir**
  - **↓↓ Cyclosporine**
  - **↓ Statins**

Ruschitzka F, et al. *Lancet.* 2000;355(9203):548-549.
Piscitelli SC, et al. *Lancet.* 2000;355(9203):547-548.

Cytochrome P-450: Enzymes and Selected Substrates

1A2	2C	2D6	3A4
Theophylline	Phenytoin	Codeine	Antihistamines
Warfarin	Warfarin	Venlafaxine	Calcium channel blockers
Antipsychotics	Amitriptyline	Trazodone	Carbamazepine
Benzodiazepines	Clomipramine	Risperidone	Cisapride
Fluvoxamine	Omeprazole	Haloperidol	Corticosteroids
	Citalopram	Tramadol	Cyclosporine
	Escitalopram	β-Blockers	Fentanyl
			Protease inhibitors
			Statins
			Triazolo-benzodiazepines

Michalets EL. *Pharmacotherapy*. 1998;18:84 -112.
Cupp MJ, Tracy TS. *Am Fam Physician.* 1998;57:107-116.

Inhibition of Human Cytochrome P-450 Isoenzymes by Newer Antidepressants

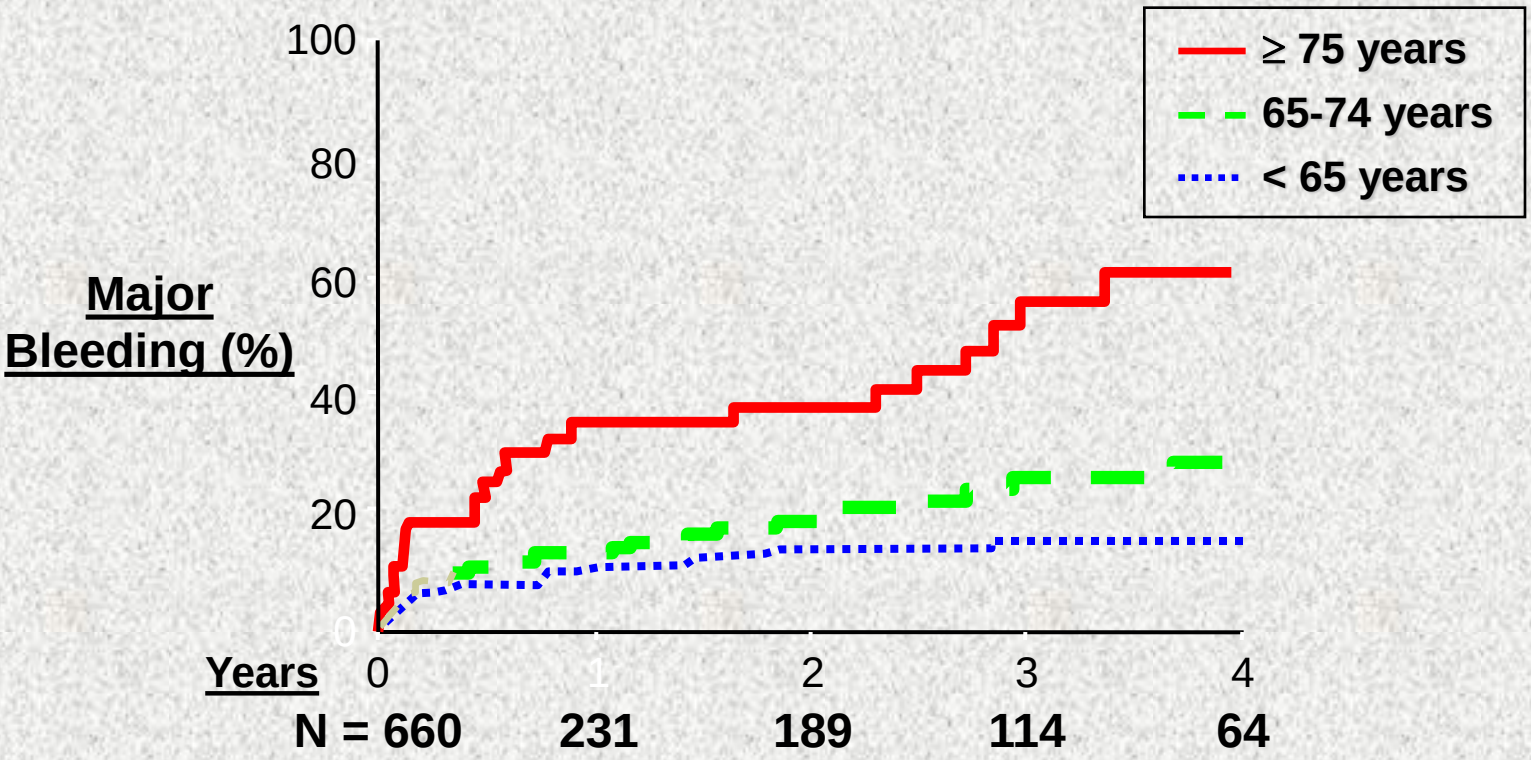
Cytochrome P-450 Isoenzyme

Antidepressant	1A2	2C9	2C19	2D6	2E1	3A
Fluoxetine	+	++	+ to ++	+++	—	+
Norfluoxetine	+	++	+ to ++	+++	—	++
Sertraline	+	+	+ to ++	+	—	+
Desmethylsertraline	+	+	+ to ++	+	—	+
Paroxetine	+	+	+	+++	—	+
Fluvoxamine	+++	++	+++	+	—	++
Citalopram	+	0	0	0	0	0
R-Desmethylcitalopram	0	0	0	+	0	0
Escitalopram	0	0	0	0	0	0
S-Desmethylcitalopram	0	0	0	0	0	0
Nefazodone	0	0	0	0	—	+++
Triazoledione	0	0	0	0	—	+
Hydroxynefazodone	0	0	0	0	—	+++
Venlafaxine	0	0	0	0	—	0
O-Desmethylvenlafaxine	0	0	0	0	—	0
Mirtazapine	0	—	—	+	—	0

0 = minimal or zero inhibition.
\+ = mild inhibition.
++ = moderate inhibition.
+++ = strong inhibition.
— = no data available.

Greenblatt DJ, et al. *J Clin Psychiatry*. 1998;59(suppl 15):19-27.
von Moltke LL, et al. *Drug Metab Disposition.* 2001;29:1102-1108.

Incidence of Bleeding During Anticoagulant Therapy



Beyth RJ, Schorr RI. *Drugs Aging*. 1999;14:231-239.

American Medical Directors Association "Top 10" Drug Interactions Includes:

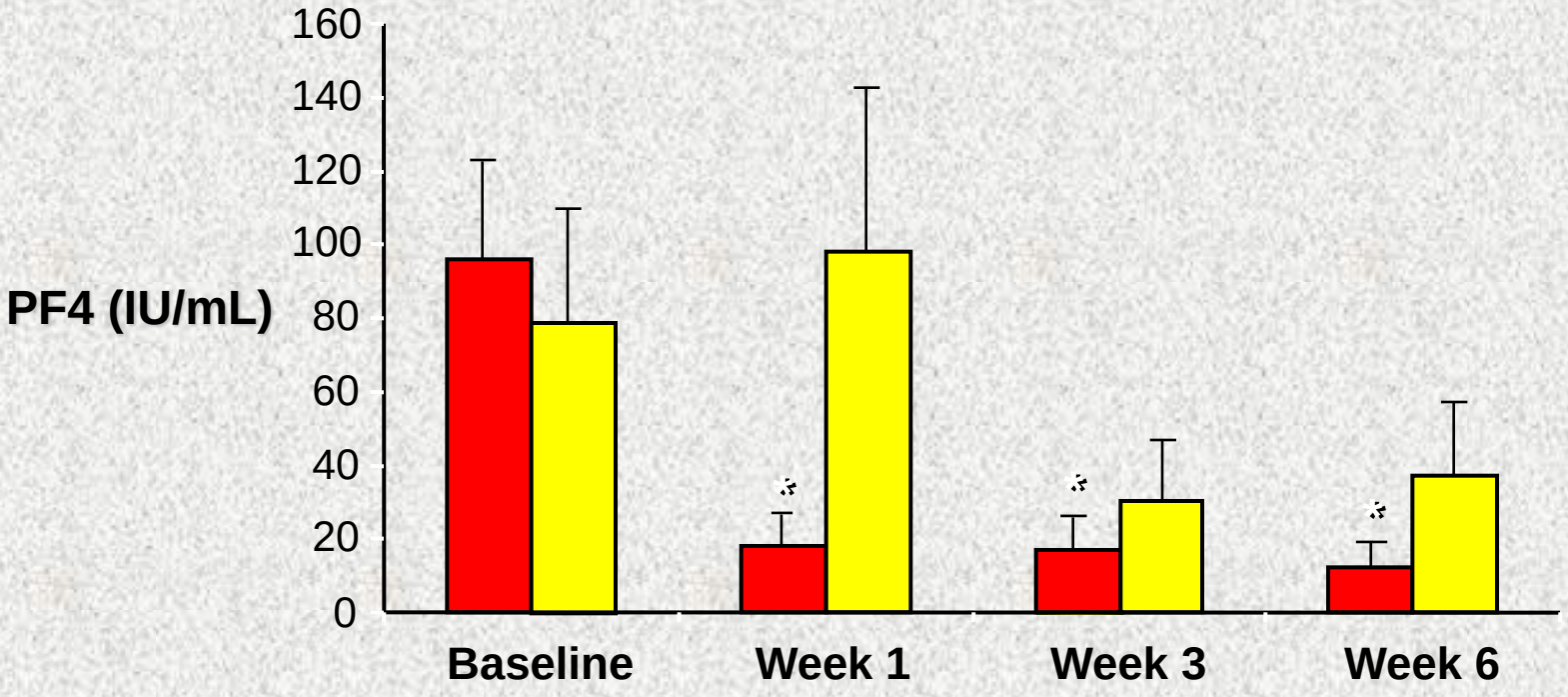
Warfarin with:

- NSAIDs
- Macrolides
- Phenytoin
- Sulfa Drugs
- Quinolones

Warfarin Metabolism

***S*-warfarin**	**CYP2C9**	**Fluoxetine** **Fluvoxamine** **(Sertraline)** **(Paroxetine)**
***R*-warfarin** **(major pathway)**	**CYP1A2**	**Fluvoxamine** **(Fluoxetine)** **(Sertraline)** **(Paroxetine)**
***R*-warfarin** **(minor pathway)**	**CYP2C19** **& CYP3A4**	

Platelet Activation in Depressed Patients With Ischemic Heart Disease After Paroxetine or Nortriptyline Treatment



❖ **Effect of paroxetine ( ) and nortriptyline ( ) on PF4 plasma levels in depressed patients with ischemic heart disease. Data presented are mean ± SEM**

***P* < .05 versus baseline levels.**

PF4 = platelet factor 4.

Pollock BG, et al. *J Clin Psychopharmacol.* 2000;20:137-140.

SSRIs & Upper GI Bleeding

- Excess GI Bleeding:
  - 3.1/1000 Tx yrs (Overall)
  - 4.1/1000 Tx yrs (>80 yrs)
  - 11.7/1000 Tx yrs (Hx prior GI bleed)

Dalton SO, Sorensen HT, et al. *CNS Drugs*. 2006; 20:143-151.

Elderly Are More Difficult to Treat Safely

- Pharmacokinetic changes result in higher and more variable drug concentrations
- The elderly often take multiple medications
- Greater sensitivity exists to a given drug concentration
- Homeostatic reserve may be impaired

When To Worry About Drug Interactions

- Multiple co-administered medications
- Narrow therapeutic index of victim
- Highly potent inducer or inhibitor

Coping With Drug Interactions

- **Anticipation and prevention**
  - **Highly potent inducer/inhibitor**
  - **Narrow therapeutic index of victim**
  - **Victims dependent on one metabolic enzyme/transport protein**

Coping With Drug Interactions

- Recognize interaction potential of “nondrugs” (herbals)
- Keep knowledge base current
- Consider interactions whenever the clinical picture unexpectedly changes

Elderly Are More Difficult to Treat Safely

- Critical lack of controlled efficacy/safety data
- Pharmacokinetic changes result in higher and more variable drug concentrations
- Concentration affects efficacy & safety (75% of ADRs are dose-related)
- Greater sensitivity exists to a given drug concentration (e.g., reductions in ACh)

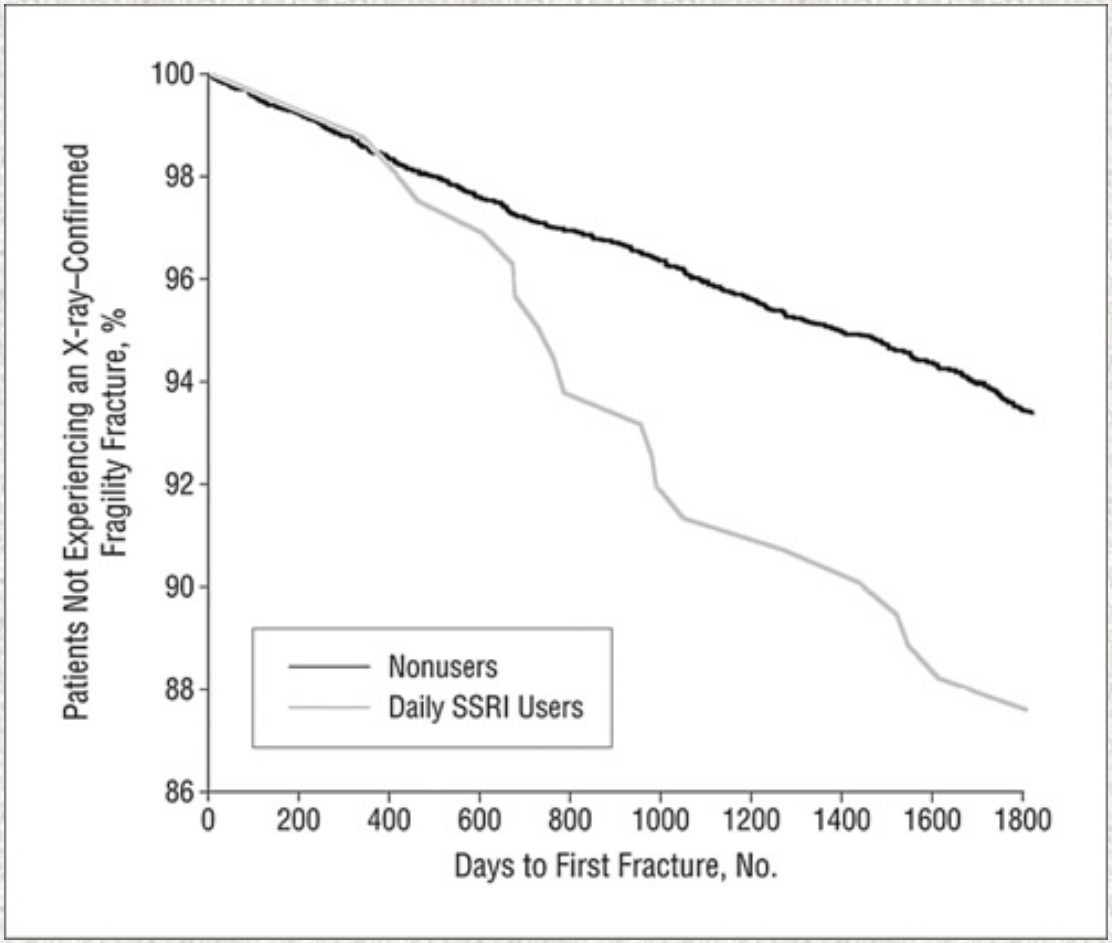
Pollock BG, Semla T, Forsyth C: Psychoactive Drug Therapy in the Elderly. In: Blass JP, Halter JB, Ouslander et al (Eds) Hazzard's Principles of Geriatrics and Gerontology. New York McGraw-Hill, pp. 767-778, 2009.

Exclusions From AD Regulatory Trials

- Exclusion criteria for two regulatory ChE trials were found to eliminate more than 90% of a community sample of 3470 subjects with possible or probable AD. Patients provisionally eligible were younger, relatively underrepresented by women, better educated, healthier, wealthier, and more likely to be white than ineligible patients. (Schneider LS. et al. Eligibility of Alzheimer's disease clinic patients for clinical trials. J Am Geriatrics Soc. 45:923-8, 1997).

- Of 11, 957 subjects 97% of subjects in cog enhancer trials were non–minority Faison WE et al. Potential ethnic modifiers in the assessment and treatment of Alzheimer's disease: challenges for the future Inter Psychogeriatri 19:539-558 2007.

SSRI Use and Risk of Fragility Fracture



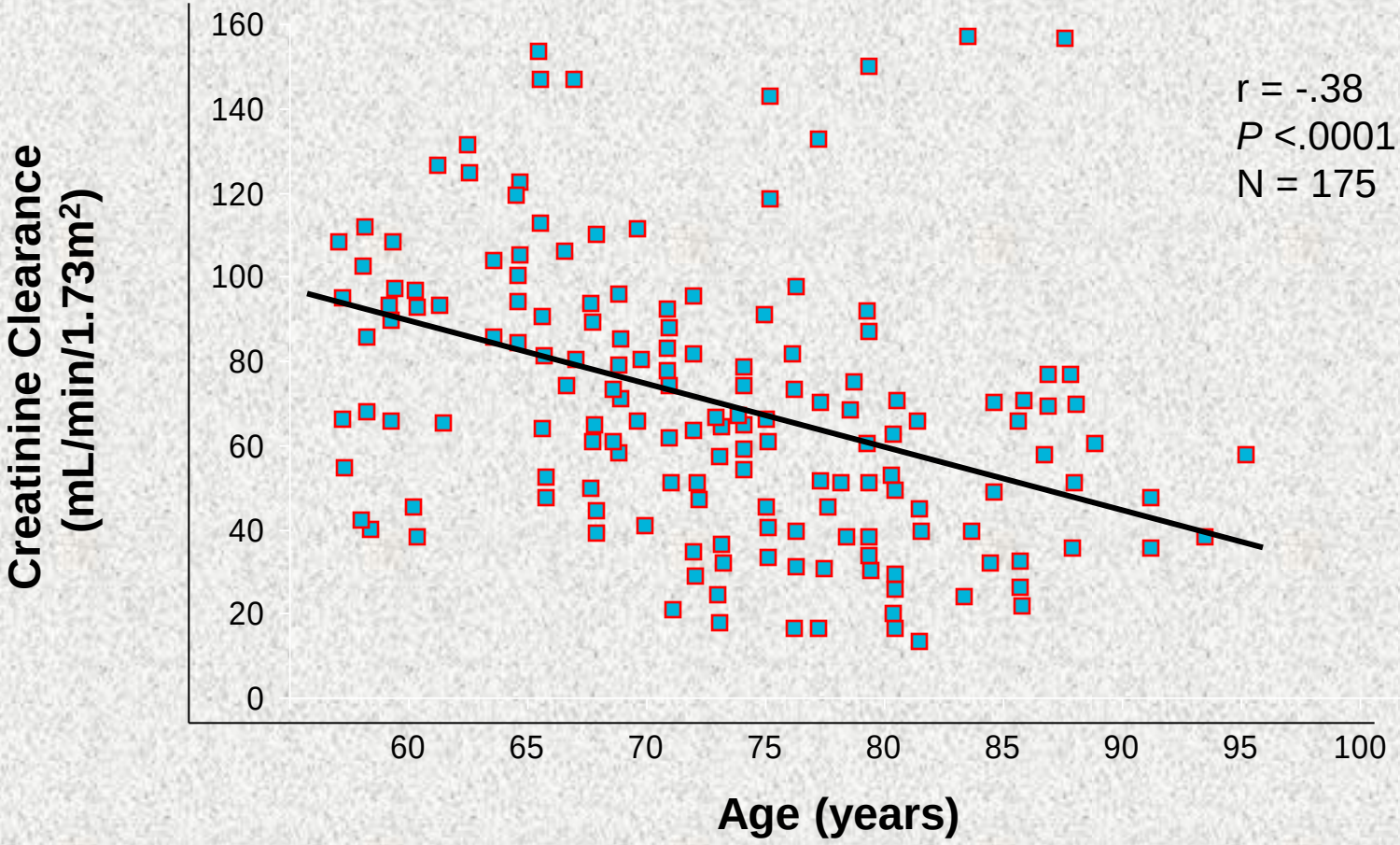
Richards JB, Papaioannou, A, et al. *Arch Int Med* 2007;167:188-194.

Changes in the Elderly

- Increased volume of distribution (increased adipose tissue)
- Decreased GFR (decreased renal clearance)
- Decreased hepatic blood flow

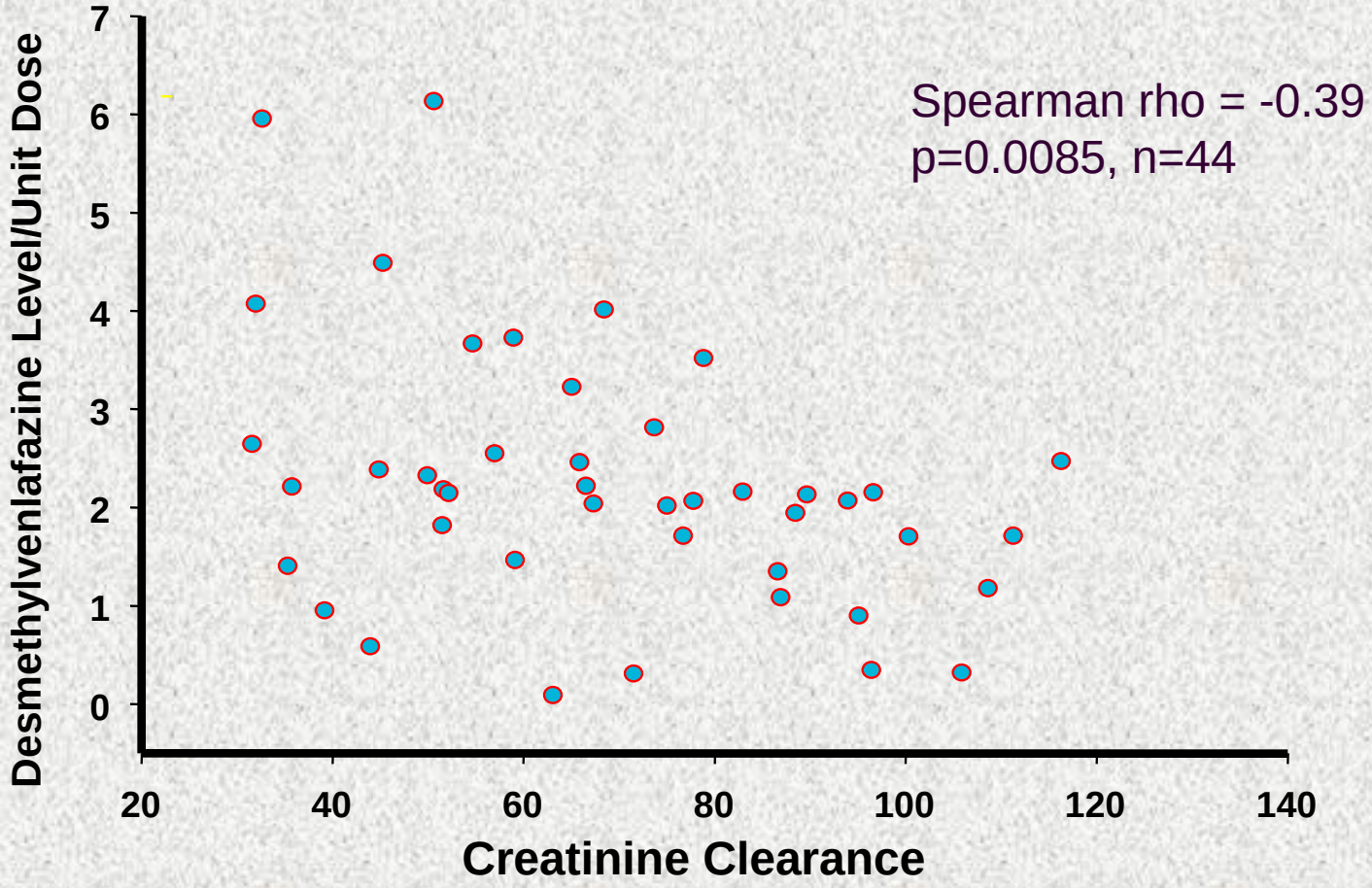
Lotrich & Pollock, J Clin Pharmacol 45:1106-1122, 2005

Decline in Creatinine Clearance With Age



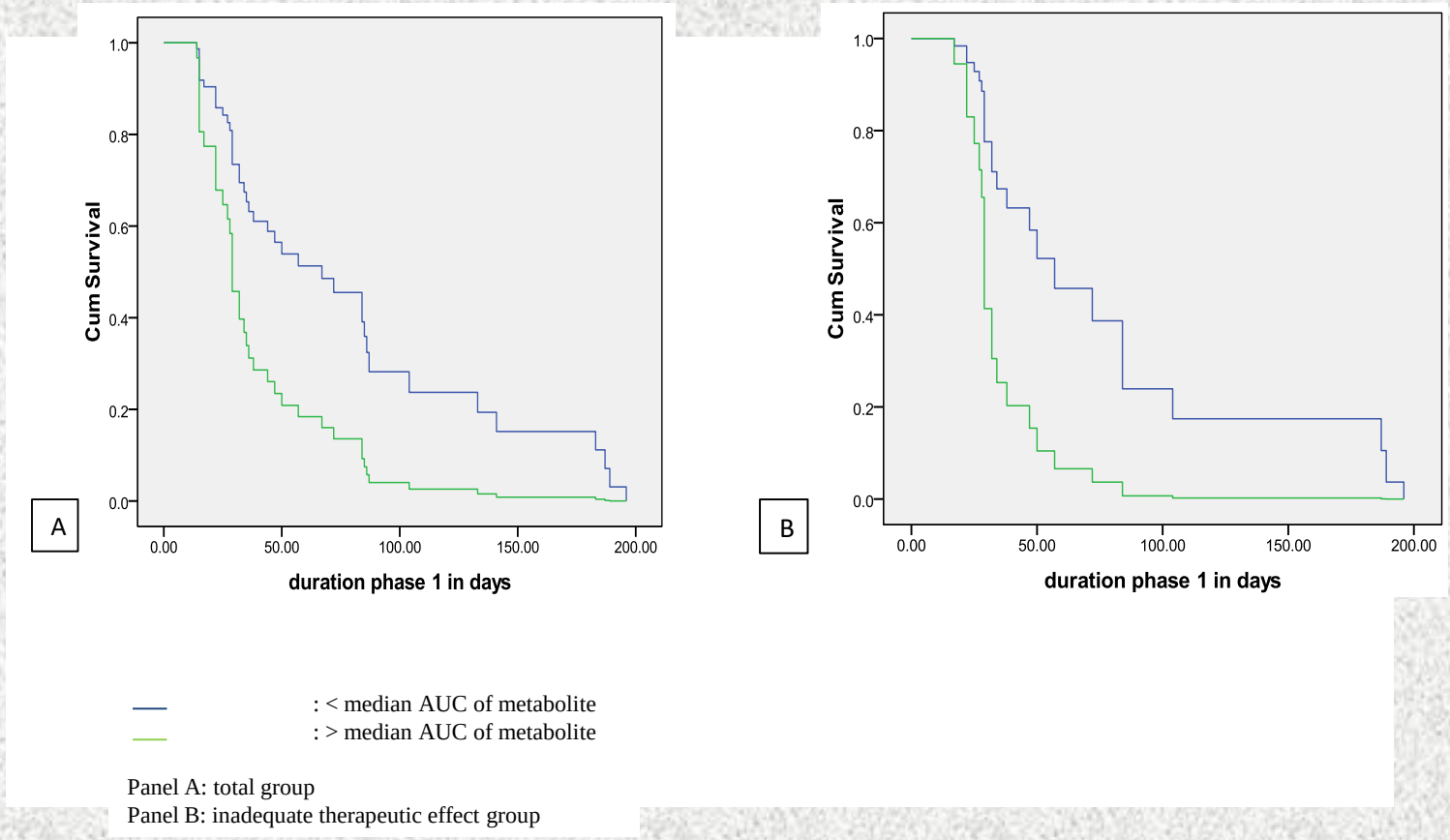
Pollock BG, et al: *Psychopharmacol Bull.* 1995; 31:327.

Creatinine Clearance and O-Desmethylvenlafaxine Level/Dose Detected in Depressed Subjects



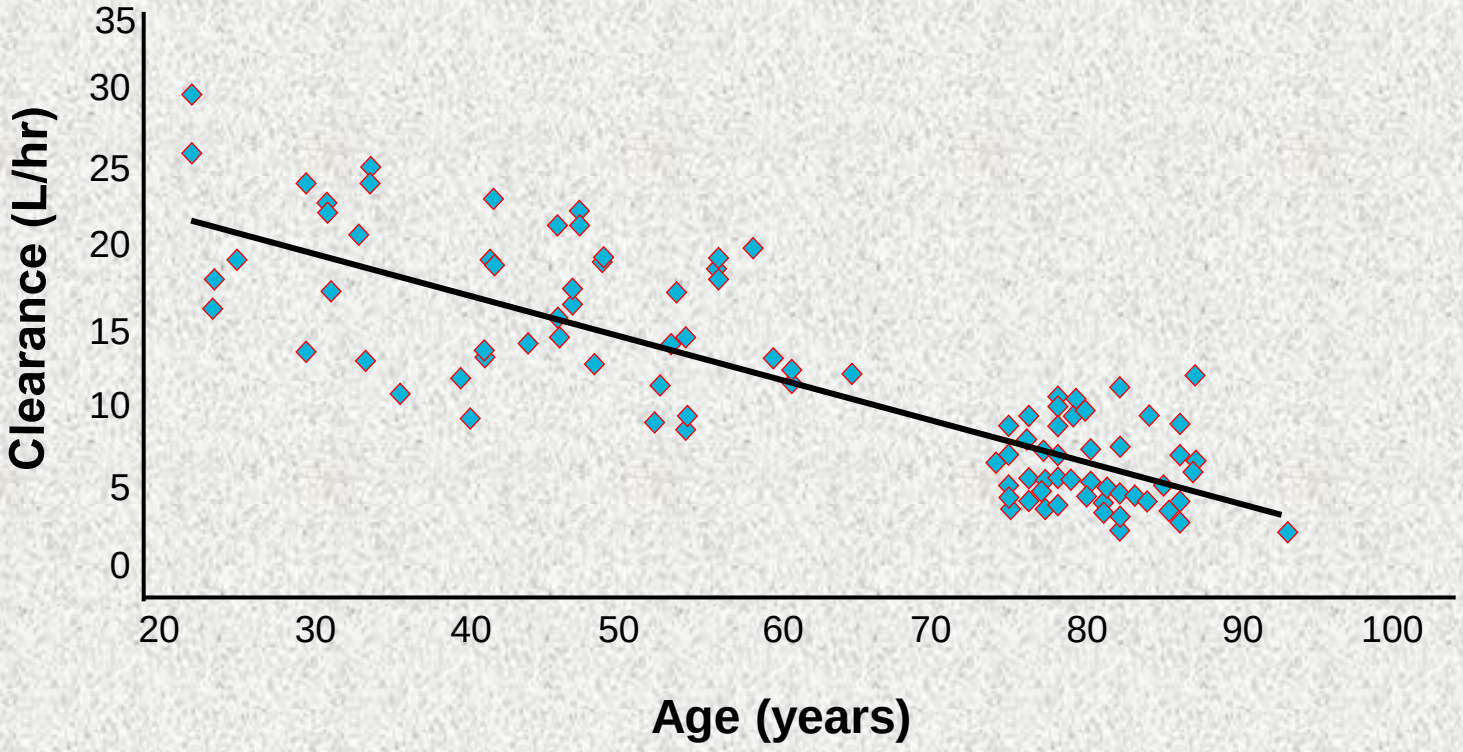
Whyte EM, Romkes M, et al., *Int J Ger Psych* 2006; 21:542-549

Association of 9-hydroxy risperidone concentrations and risk of switching or discontinuation in the CATIE AD trial



Wessels AM, Pollock BG et al. Journal of Clinical Psychopharmacology 30: 683-687, 2010

Individual Citalopram Clearance vs. Age



Bies RR, Pollock BG, et al. *J Clin Pharmacol.* 2004;44:1352-1359.

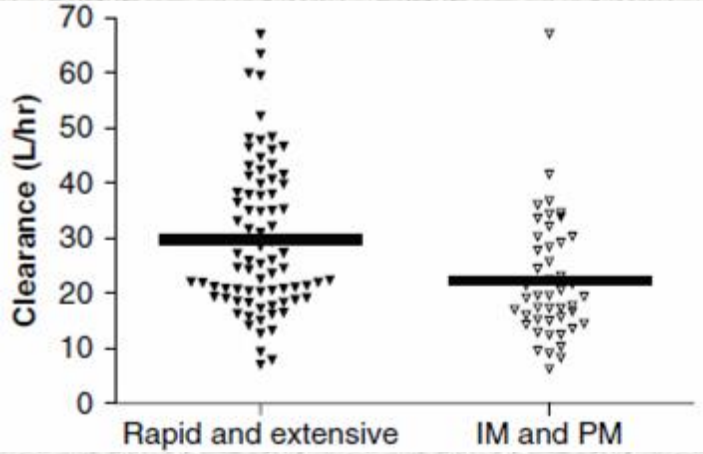
FDA Advisory August 2011

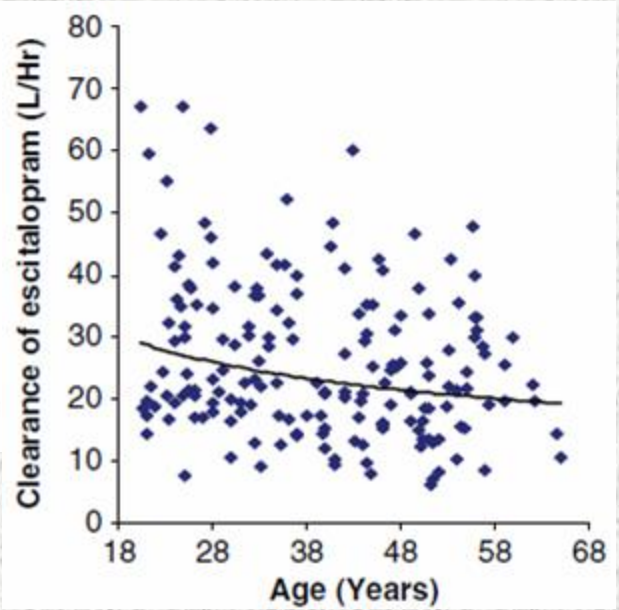
Citalopram 20 mg per day is the maximum recommended dose for patients:

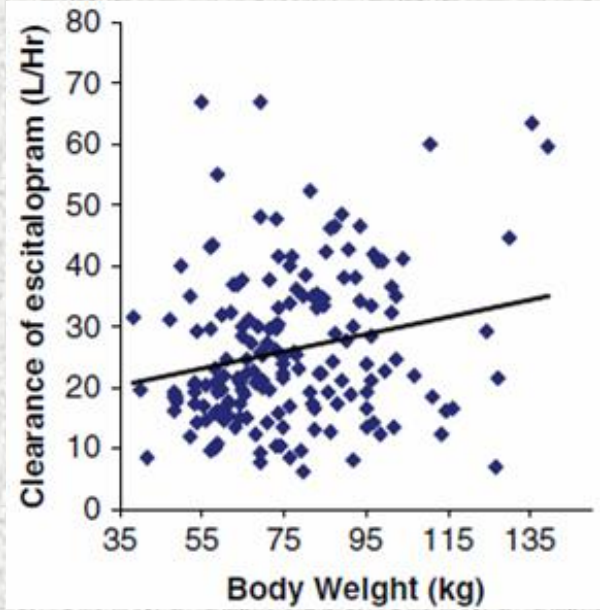
- With hepatic impairment
- Greater than 60 years of age who are CYP2C19 poor metabolizers
- Taking concomitant cimetidine (Tagamet®)

These factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes.

Effect of Age, Weight, and CYP2C19 Genotype on Escitalopram Exposure

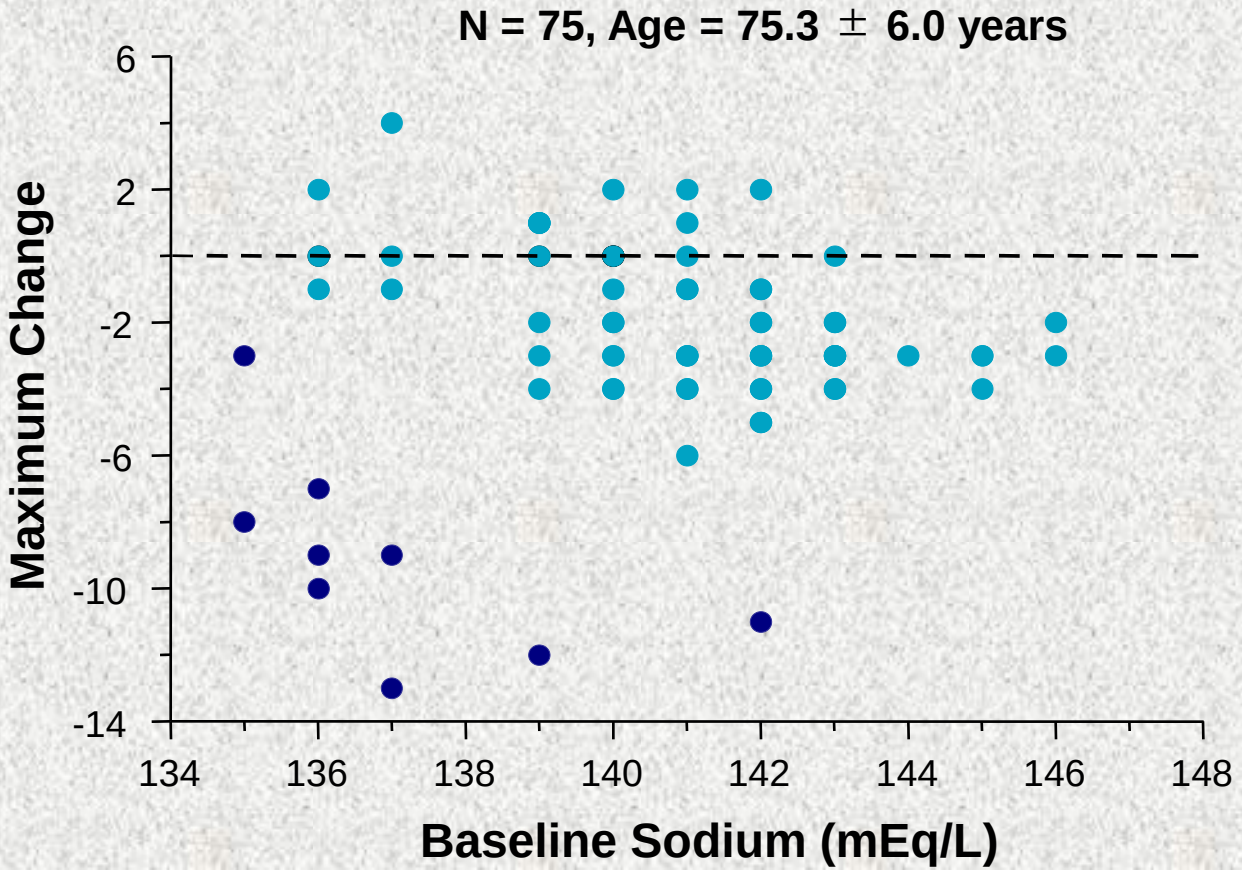






Jin Y, Pollock BG et al. J Clin Pharmacol 50: 62-72, 2010.

Paroxetine-Induced Hyponatremia in Older Adults: a 12-week Prospective Study



Fabian TJ, Pollock BG, et al. *Arch Intern Med*. 2004;164(3):327-332.

Drug-Related Morbidity & Mortality (the most frequent treatable illness in older patients)

- >65 years, 13% of population, 40% of prescriptions
- Adverse reactions to drugs (ADRs) are 7-10 X higher in 70 to 79 y.o. than in those who are 20-29 y.o.
- 20% of hospital admissions > 70 have been attributed to ADRs. ADRs account for only 3% admissions in rest of population.
- Morbidity & mortality associated with drug-related problems cost $4 billion/year in U.S. long-term care.
- Psychoactive medications and anticoagulants are the most common medications associated with preventable ADRs

Laroche et al.Br J Clin Pharmacol 2007; 63: 177.
Gurwitz, et al. *Am J Med.* 2000; 109(2):87-94

Anticholinergic Drugs

- Leading cause of delirium in elderly
- Potent anticholinergic medications
  - Amitriptyline
  - Clozapine
  - Diphenhydramine
  - Oxybutynin
- Effects of mildly anticholinergic drugs may be cumulative

AA and Cognitive Impairment Associated in:

- **Younger patients** (typically with schizophrenia): **4 of 7** published studies (N = 157)
- **Older patients** (typically with delirium or dementia): **13 of 14** published studies (N = 623)

Chew, Mulsant et al (2005) Am. J.Geri. Psychiatry; 13:535-8
Chew, Mulsant et al (2007) Schizophrenia Research

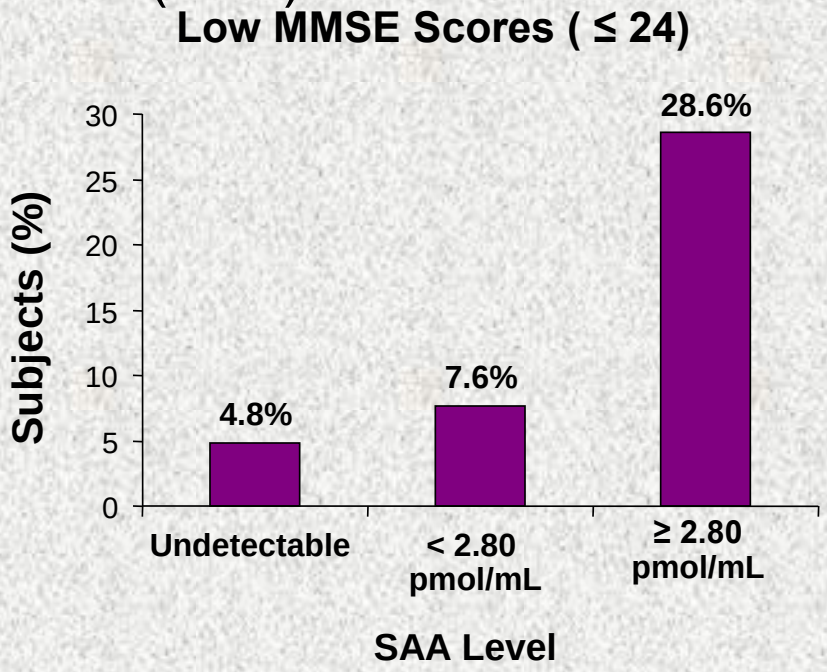
Measuring Anticholinergic Activity (AA) with a Radioreceptor Assay

- Tritiated quinuclidinyl benzilate (3H-QNB): high and specific affinity for muscarinic receptors
- Anticholinergic compounds competitively inhibit 3H-QNB binding to muscarinic receptors
- Displacement of 3H-QNB bound to an homogenate of rat forebrain used to quantify AA
- AA in picomoles of atropine equivalents per mL (pmol/mL or nM) based on amount of 3H-QNB displacement caused by a standard amount of atropine
- AA reflects the cumulative anticholinergic effect of all exogenous substances taken by the subject (i.e., medications and supplements) and their metabolites

Tune & Coyle (1980); Mulsant et al (2003)

SAA & Cognitive Performance in a Community-Based Sample of Older Adults

- Subjects with higher serum anticholinergic activity have lower MMSE scores (≤ 24)



SAA Level (pmol/mL)	Odds Ratio
Undetectable	1.00 (reference)
0.25–2.79	2.01 (CI: 0.22–18.53)
≥ 2.80	12.81 (CI: 1.08–152.39)

SAA = serum anticholinergic activity; CI = confidence interval.

Mulsant BH, Pollock BG, et al. *Arch Gen Psychiatry.* 2003;60:198-203.

Anticholinergic Activity of 107 Medications Commonly Used by Older Adults

- Cimetidine Codeine
- Digoxin Dipyridamole
- Diphenhydramine
- Furosemide
- Nifedipine
- Olanzapine
- Oxybutynin
- Paroxetine Prednisolone
- Ranitidine
- Theophylline
- Warfarin

.

Chew ML, et al. J. Am Geriatrics Soc 56: 1333-1341, 2008.

Suggested Readings

DeVane CL, Pollock BG: Pharmacokinetic considerations of antidepressant use in the elderly. J Clin Psychiatry 60[suppl 20]:38-44, 1999.

Lotrich FE, Pollock BG: Aging and clinical pharmacology: Implications for antidepressants. J Clin Pharmacol 45:1106-1122, 2005.

Chew ML, Mulsant BH, **Pollock BG**, Lehman ME, Greenspan A, Mahmoud RA, Kirshner MA, Sorisio DA, Bies RR, Gharabawi G: Anticholinergic Activity of 107 Medications Commonly Used by Older Adults. J Am Geriatrics Soc, 56: 1333-1341, 2008.

Pollock BG: Treatment of Psychiatric Disorders: General Principles. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Ninth Edition. Philadelphia, PA: Lippincott Williams & Wilkins, pp 4101-4105, 2009.

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Self Assessment Question Answers

- 1. C
- 2. D
- 3. D
- 4. E
- 5. E